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Enfuvirtide, an HIV-1 fusion inhibitor peptide, can act as a potent SARS-CoV-2 fusion inhibitor: an *in silico* drug repurposing study

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ABSTRACT

Regarding the urgency of therapeutic measures for coronavirus disease 2019 (COVID-19) pandemic, the use of available drugs with FDA approval is preferred because of the less time and cost required for their development. *In silico* drug repurposing is an accurate way to speed up the screening of the existing FDA-approved drugs to find a therapeutic option for COVID-19. The similarity in SARS-CoV-2 and HIV-1 fusion mechanism to host cells can be a key point for Inhibit SARS-CoV-2 entry into host cells by HIV fusion inhibitors. Accordingly, in this study, an HIV-1 fusion inhibitor called Enfuvirtide (Enf) was selected. The affinity and essential residues involving in the Enf binding to the S2 protein of SARS-CoV-2, HIV-1 gp41 protein and angiotensin-converting enzyme 2 (ACE-2) as a negative control, was evaluated using molecular docking. Eventually, Enf-S2 and Enf-gp41 protein complexes were simulated by molecular dynamics (MD) in terms of binding affinity and stability. Based on the most important criteria such as docking score, cluster size, energy and dissociation constant, the strongest interaction was observed between Enf with the S2 protein. In addition, MD results confirmed that Enf-S2 protein interaction was remarkably stable and caused the S2 protein residues to undergo the fewest fluctuations. In conclusion, it can be stated that Enf can act as a strong SARS-CoV-2 fusion inhibitor and demonstrates the potential to enter the clinical trial phase of COVID-19.

Abbreviations: ACE-2: angiotensin-converting enzyme 2; Enf: Enfuvirtide; FDA: Food and Drug Administration; HIV: human immunodeficiency virus; MD: molecular dynamics; RBD: receptor binding domain

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1. Introduction

The outbreak of coronavirus disease 2019 (COVID-19) which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was started from the Wuhan (China) (Arshad Ali et al., 2020; Li & Liu, 2020). Afterward, the terrible disease rapidly spread all over the world so that by December 25, 2020, more than 79.4 million people have been confirmed to be infected with SARS-CoV-2 and more than 1,740,000 deaths due to COVID-19 have been recorded worldwide (Chen, 2020; Li & Liu, 2020). On 11th March 2020, WHO declared COVID-19 as a pandemic due to its high contagion and mortality rate (Cucinotta & Vanelli, 2020). No approved vaccine or effective drug has been reported for COVID-19 yet (Bhagavathula et al., 2020). Regarding the urgency of therapeutic measures for COVID-19, the use of available drugs with FDA approval is preferred because they need to the less time and cost for the evaluation and development (Durojaiye et al., 2020). Computer-aided drug repurposing represents an accurate strategy to speed up the screening of existing drugs with FDA approval to find the suitable treatment options for COVID-19 (Ciliberto & Cardone, 2020; Wang, 2020). Similar to SARS-CoV, SARS-CoV-2 is an enveloped positive-strand RNA virus (Romano et al., 2020). The cell surface receptor of both viruses is angiotensin-converting enzyme 2 (ACE-2), however the apparent affinity of SARS-CoV-2 to ACE-2 is 10 to 20 times higher than that of SARS-COV (Fani et al., 2020). The genetics alignments showed that the SARS-CoV-2 genome had 88–89% similarity to two other bats-derived SARS-like coronaviruses namely bat-SL-CoVZC45 and bat-SL-CoVXC21. Also, 82 and 50% of the SARS-CoV-2 genome is similar to SARS-CoV and MERS-CoV genomes, respectively (Lai et al.,

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